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(54) Title: NANOPARTICLES IN PHOTODYNAMIC THERAPY

(57) Abstract

The present invention relates to a pharmaceutical composition in the form of an aqueous dispersion of nanoparticles comprising the zinc phthalocyanine complex and a polymer which is suitable for the formation of nanoparticles, to a process for the preparation of said pharmaceutical composition and to the therapeutic use thereof, e.g. in photodynamic therapy.

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Nanoparticles in Photodynamic Therapy

The present invention relates to a pharmaceutical composition comprising the zinc phthalocyanine complex and a polymer which is suitable for the formation of nanoparticles, to a process for the preparation of said pharmaceutical composition and to the therapeutic use thereof, e.g. in photodynamic therapy.

Both the zinc phthalocyanine complex and its therapeutic use in photodynamic therapy for the treatment of tumors are known, q.v. *J.D.Spikes, Photochem. Photobiol. 43, 691 (1986).* The zinc phthalocyanine complex is administered in vivo intraperitoneally to mice or rats in the form of an aqueous suspension, and the carcinoma induced in experimental animals is irradiated with high-energy light, preferably with concentrated visible light (LASER).

The use of intraperitoneal dosage forms in human therapy is considered inacceptable in view of serious pains caused when piercing the abdominal cavity. The skillful use of the injection syringe in this difficult mode of administration is strictly mandatory for the practicing physician. Several attempts have, therefore, been made to find safer and better dosage forms which are more acceptable to the patient and the administering physician.

The intravenous dosage form allows the systemic distribution of the active ingredient, but requires solubility of the active agent in the aqueous injection fluid. The zinc phthalocyanine complex, however, is characterized by extremely low water solubility and insolubility in almost all organic solvents. As an exception to this observation, it has been found that the zinc phthalocyanine complex is soluble in some selected polar aprotic agents such as dimethyl sulfoxide, N-methyl-2-pyrrolidone or pyridine.

To overcome these solubility problems, it has been proposed to solubilize the zinc phthalocyanine complex in the aqueous phase by the addition of a vehicle. By using, for example, phospholipids as solubilizers, the complex can be solubilized by encapsulation in unilamellar liposomes which are homogeneously dispersible in aqueous phase, q.v. *Reddi et al., Br. J. Cancer , Vol. 56, pages 597-600 (1987).*

This homogeneous liposome dispersion is nevertheless still unsuitable for the purposes of intravenous administration to humans because the dispersion is prepared in accordance with the so-called injection method using relatively large amounts of toxic pyridine, q.v. *G. Valduga et al., J. Inorg. Biochem. 59-65, Vol. 29 (1987).*

Pyridine is one of the few solvents in which the zinc phthalocyanine complex is at all soluble. That solution is diluted with ethanol, and the pyridine-containing ethanolic solution is injected at elevated temperature into water or a buffer solution. In accordance with that method, a residue of the organic solvent will permanently remain in the aqueous phase as a result of the formation of an azeotropic mixture, even if the toxic solvent pyridine is replaced by less toxic organic solvents such as dimethyl sulfoxide or N-methyl-2-pyrrolidone.

The encapsulation of the zinc phthalocyanine complex in liposomes formed from a phospholipid mixture of selected phospholipids is disclosed in *U.S. Patent Specification 5,270,053*. A solvent-free dry preparation containing a homogeneous mixture of a synthetic, substantially pure phosphatidyl choline derivative with a synthetic, substantially pure phosphatidyl serine derivative as well as the zinc phthalocyanine complex is dispersed in an aqueous phase, and a liposome dispersion, primarily multilamellar liposomes, is subsequently formed which is intravenously applicable.

These methods of encapsulating a pharmaceutical agent of low water-solubility in liposomes, as well as other proposed methods, such as the incorporation in micelles, mixed micelles, reversed micelles, microcapsules or microspheres have the clear advantage of improved solubilization. Unfortunately, these advantages are again diminished by a range of problems, including the low stability of the aqueous systems owing to the separation of the phase into the individual components, insufficient amounts of encapsulated active agent, the strong dependency of the particle size on the method employed, unsatisfactory uniformity and insufficient reproducibility of the products obtained, and other problems.

Surprisingly, it has now been found that the zinc phthalocyanine complex is encapsulated in pharmaceutically effective amounts in nanoparticles formed from selected pharmaceutically acceptable polymers. Accordingly, the following invention relates to a pharmaceutical composition which is suitable for the solubilization of the zinc phthalocyanine complex. The composition is characterized by the following components:

a) the zinc phthalocyanine complex;
b) a pharmaceutically acceptable polymer which is suitable for the formation of nanoparticles and, optionally;
c) further pharmaceutically acceptable additives which are suitable for incorporation in a dosage form for the intended mode of administration.

The pharmaceutical composition according to the present invention has the benefit of providing enhanced solubilization of the zinc phthalocyanine complex and specific release in selected target regions of malignant tissues such as neoplasms. This renders the pharmaceutical composition particularly useful for use in photodynamic therapy.

The general terms used throughout the specification of this invention are preferably defined as follows:

The term "pharmaceutical composition" means a mixture containing the zinc phthalocyanine complex that can be administered to a host in a therapeutic method of treating the disease or condition indicated. The composition is especially suitable for parenteral administration, especially i.v., but also for topical administration.

The term "solubilization" defines the homogeneous dispersion of the zinc phthalocyanine complex of extremely low water solubility in an aqueous phase containing nanoparticles with the aid of a pharmaceutically acceptable solubilizer which is suitable for the preparation of nanoparticles.

Nanoparticles are solid spheroid particles ranging in size from about 10 to 1000 nm. When dispersed in an aqueous phase, they have colloidal properties. The term nanoparticles is a generic term that comprises nanospheres and nanocapsules. Nanospheres have a polymeric matrix type structure, whereas nanocapsules have a shell formed of polymers surrounding a liquid core. Nanoparticles encapsulate the zinc phthalocyanine complex of extremely low water solubility.

The term "encapsulation" indicates the presence of the active agent zinc phthalocyanine in nanoparticles. In nanospheres, the active agent may be adsorbed at their surface or entrapped, e. g. as microcrystals, in the polymeric matrix, or may be dissolved therein. In nanocapsules the active agent may be dispersed in the liquid present in the core, but may also be adsorbed at the surface, entrapped or dissolved in the polymeric matrix.

Component a) - active agent: the zinc phthalocyanine component is listed as "ciaftalan zinc" in List 74 of proposed INNs (International Nonproprietary Names) published in the *Vol.9, No.4 (1995)* issue of the *WHO Drug Information.*

Component b) - polymers: a pharmaceutically acceptable polymer which is suitable for the formation of nanoparticles is, for example, a pharmaceutically acceptable homopolymer or copolymer from monomers selected from the group consisting of L-lactide N or S, D-lactide

S, D,L-lactide S, glycolide S or trimethylene carbonate. Those polymers are marketed under the trade-mark MEDISORB (Registered Trade-Mark of Medisorb Technologies Inc.), PURASORB (Registered Trade-Mark of PURAC Biochem.) or RESOMER (Registered Trademark of Boehringer Ingelheim, Germany).

Suitable products are MEDISORB polymers of the L or DL series, e.g. 100 L or DL, or 8515, 7525, 6535, or 5050 DL, or RESOMER homopolymers of the L series, formed from L-lactide, e.g. L 104, 206 - 210, or 214, R series formed from racemic D,L-lactide, e.g. R 104, 202, 203, or 206 - 208 or G series formed from glycolide, e.g. G 205, or copolymers of the LR series formed from L-lactide with D,L-lactide, e.g. LR 708, or 909 or DL-lactide with glycolide, e.g. RG 502 - 505, 752, 755, 756, or 858.

Whenever other modes of administration, such as topical administration, are intended, other polymers suitable for the formation of nanoparticles may be selected. An alternative polymer is a pharmaceutically acceptable copolymer formed from monomers selected from the group consisting of methacrylic acid, methacrylic acid esters, acrylic acid and acrylic acid esters. These polymers are commercially available from Röhm Pharma GmbH, Weiterstadt, Germany, and are marketed under the trademark EUDRAGIT (Registered Trademark of Röhm Pharma GmbH).

An especially preferred polymer of the EUDRAGIT series is the 1:1- to 1:2-copolymer which is formed from monomers selected from the group consisting of methacrylic acid and methacrylic acid lower alkyl esters, such as the 1:1- to 1:2-copolymer of methacrylic acid and methyl methacrylate. The 1:1-copolymers are marketed in the EUDRAGIT L series, such as L 12.5, 100, or L 30 D. The corresponding 1:2-copolymers are marketed in the EUDRAGIT S series, such as S 12.5 or S 100.

Another preferred polymer of the EUDRAGIT series is the 1:1- copolymer of methacrylic acid and acrylic acid ethyl ester. This polymer is marketed under the product name EUDRAGIT L 100-55.

Another polymer which is suitable for the formation of nanoparticles is polyvinyl acetate phthalate (PVAP) or a pharmaceutically acceptable cellulose derivative selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate (HPMCAS), hydroxypropyl methyl cellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), and cellulose acetate trimellitate (CAT).

HPMCP is marketed by Eastman Kodak Corp.. HPMCP 50 (USP/NF type 220824) and HPMCP 55 (USP/NF type 200731) are especially preferred.

CAP is marketed under the trademark AQUATERIC (Registered Trademark of FMC Corp.) or is commercially available from Eastman (composition: phthalyl 35 %, acetyl 24 %, moisture 1 %, free acid 0.5 % (as phthalic acid)).

CAT is commercially available from Eastman (composition: trimellityl 29 %, acetyl 22 %, moisture 1 %, free acid 0.5 % (as phthalic acid)).

Component c) - additives: Pharmaceutically acceptable additives are determined by the dosage form for the intended mode of administration. A preferred mode of administration is parenteral, especially i.v., but also topical, e.g. ocular.

Parenteral dosage forms are particularly useful for intravenous, but also for intramuscular administration. If intravenous administration is intended, water is added that has been sterilized and freed from pyrogens, according to the prescriptions of national pharmacopoeias, such as *The U.S. Pharmacopoeia (USP)* or *Deutsches Arzneibuch (DAB)*. The addition of water-soluble additives, which are suitable for the adjustment of isotonic conditions, is particularly preferred, typically sodium chloride, sorbitan, mannitol, glucose, lactose or fructose. If intramuscular administration is intended, oily carrier liquids, such as sesame oil or olive oil, but also lecithin, may be added.

Additives for topical formulations are listed in standard textbooks, e.g. Remington's Pharmaceutical Sciences or *Hagers Handbuch der Pharmazeutischen Praxis*. Topical formulations are in particular creams, ointments, gels, pastes or topically administered aerosols and also suspensions of nanoparticles or ophthalmic compositions.

Suitable additives for topical and especially ophthalmic compositions are in particular inert carriers, solubilizers, tonicity-increasing agents, buffer substances, preservatives, thickeners, and other adjuncts. Such additives are e.g. ethanol, vegetable oil, mineral oil containing hydroxyethyl cellulose, ethyl oleate, carboxymethyl cellulose, polyvinylpyrrolidone, and other non-toxic water-soluble polymers intended for ophthalmic use, e.g. cellulose ethers such as methyl cellulose, alkali metal salts of carboxymethyl cellulose or hydroxymethyl, hydroxyethyl, or hydroxypropyl cellulose, acrylates or methacrylates such assalts of polyacrylic acid or ethyl acrylate, polyacrylamides, natural products such as gelatin, alginates, pectins, tragacanth, karaya gum, xanthan gum, carrageenan, agar or acacia, starch derivatives such as starch acetate and hydroxypropyl starch, and also other

synthetic additives such as polyvinyl alcohol, polyvinylpyrrolidone, polyvinyl methyl ether, polyethylene oxide, preferably crosslinked polyacrylic acid such as neutral Carbopol® or mixtures of these polymers.

Examples of buffer substances are acetate, ascorbate, borate, bicarbonate/ carbonate, citrate, gluconate, lactate, phosphate, propionate, and so-called tris buffers. The amount of buffer substance is added to maintain a physiologically acceptable pH-range.

Tonicity-enhancing agents are, for example, ionic compounds, such as alkali metal or alkaline earth metal halides, e.g. $CaCl_2$, Kbr, KCl, LiCl, NaI, NaBr, or NaCl, or boric acid. Non-ionic tonicity-enhancing agents are, for example, urea, glycerol, sorbitol , mannitol, propylene glycol, or dextrose. Sufficient tonicity-enhancing agent is added that the ophthalmic composition has an osmolality in a preferred range of about 50 to 400 mOsmol.

Examples of preservatives are quaternary ammonium salts such as cetrimide, benzalkonium chloride, alkylmercury salts of thiosalicylic acid such as thiomersal, phenylmercury nitrate, acetate, or borate, parabens such as methylparaben or propylparaben, alcohol, e.g. chlorobutanol, benzyl alcohol, or phenylethanol, guanidine derivatives, e.g. chlorhexidine, or polyhexamethylenebiguanide, or sorbic acid. If desired, the amount of preservative which is necessary to ensure sterility is added to the ophthalmic composition.

The present invention in particular relates to a pharmaceutical composition suitable for intravenous administration and containing

a) the zinc phthalocyanine complex;
b) a pharmaceutically acceptable homopolymer or copolymer from monomers selected from the group consisting of L-lactide N or S, D-lactide S, D,L-lactide S, or glycolide S;
c) further pharmaceutically acceptable additives which are suitable for incorporation in a dosage form for intravenous administration.

The present invention also relates to a process for the preparation of said pharmaceutical composition which is characterized in that an aqueous dispersion of nanoparticles is formed containing

a) the zinc phthalocyanine complex;
b) a pharmaceutically acceptable polymer which is suitable for the formation of nanoparticles;

and the dispersion is processed further with the optional addition of pharmaceutically acceptable additives c), which are suitable for incorporation into a dosage form for the intended mode of administration.

Various methods of performing this process are known. They are compiled in *Eric Allémann et al., Eur. J. Pharm. Biopharm. 39(5), 173 - 191 (1993).* The methods for the preparation of nanospheres mentioned in this reference are particulary preferred.

An especially preferred method comprises the preparation of an aqueous gel containing a hydrophilic polymer with the optional addition of a water-soluble salt. This gel is mixed with a solution of an organic solvent containing the active agent and the polymer which is suitable for the formation of nanoparticles. Phase separation is then observed, and, after addition of water, the nanoparticles formed are homogeneously dispersed in the aqueous phase. The aqueous phase is then processed further to the pharmaceutical dosage form intended, e.g. by applying conventional purification and separation methods.

The preparation of the aqueous gel containing the hydrophilic polymer is disclosed in E. Allémann, loc. cit., and the additional references cited therein. The gel is formed by adding water to the hydrophilic polymer. Suitable hydrophilic polymers are polyvinyl alcohols such as the ones marketed under the trademark MOWIOL (Registered Trademark of Hoechst AG, Germany). Preferred are polyvinyl alcohols having a degree of hydrolysis of more than 70 % (partially hydrolized grades), especially more than 87 %, e.g. MOWIOL of the 88 and 92 series, e.g. 4-88, 5-88, 8-88, 18-88, 23-88, 26-88, and 40-88. To facilitate the separation of the phase from the organic phase, which is subsequently added, it is preferred to add to the gel phase a physiologically acceptable water-soluble salt, e.g. magnesium chloride, or magnesium acetate.

The gel phase is added, with stirring, to a solution of the organic solvent, e.g. acetone or benzyl alcohol, which contains the active agent, e.g. the zinc phthalocyanine complex and the pharmaceutically acceptable polymer, which is suitable for the formation of nanoparticles defined above.

Pure water is then added to allow diffusion of the organic solvent into the aqueous phase, and the nanoparticles are formed and homogeneously dispersed therein. The aqueous phase may be processed further by conventional purification and separation methods resulting in the preparation of the dosage form desired.

The dispersion so obtained may be defined as an aqueous suspension of nanoparticles containing zinc phthtalocyanine. According to the preferred method of phase separation of the aqueous gel from the organic solvent, a homogeneous dispersion of nanospheres is obtained. Nanospheres are clearly distinguishable by physical methods, such as photon correlation spectroscopy (PCS), e. g. with a COULTER NANO-SIZER, by LASER light scattering methods or electron microscopy, from other microparticles, such as liquid crystals, micells, reversed micells, liposomes, microspheres or microcapsules. For a statistical average of more than 80 %, preferably more than 90 %, a mean average particle size between 60 and 300 nm has been determined. The size of the nanoparticles obtained depends on the established and known methods chosen for their preparation.

The homogeneous aqueous dispersion containing nanospheres is then processed further to a conventional pharmaceutical dosage form by applying standard purification methods, e.g. the ones known in the art for purifying nanoparticles, e.g. ultracentrifugation or cross-flow filtration. The dispersion can also be lyophilized in conventional manner, and the lyophilisate is then reconstituted to the pharmaceutical dosage form desired. Even after reconstituting the lyophilisate, a homogeneous nanodispersion is formed again. When preparing lyophilisates, the addition of specific amounts of water-soluble additives is recommended.

The invention also relates to the use of the pharmaceutical composition in a method for treating the human or animal body by photodynamic therapy. The composition is administered, preferably intravenously, in a range of 0.01 - 1,00 mg/kg, preferably 0.03 - 1.0 mg/kg active substance. In photodynamic therapy, the patient is exposed 20 min.- 24 h after drug administration to a high energy light source of about 671 nm wavelength.

A parenteral dosage form is prepared by applying known methods such as the ones mentioned in *Hagers Handbuch der Pharmazeutischen Praxis* or *Remington's Pharmaceutical Sciences*. In particular the additives customarily used for the preparation of parenteral dosage forms may be added if necessary. Their choice depends on the type of dosage form requested, e.g. intravenous or intramuscular dosage forms.

The homogeneous dispersion, optionally after concentration to standardized volumes, or the lyophilisate is added to suitable containers for unitary dosage forms such as vials.

The following Example illustrates the invention as disclosed in the instant specification without limiting the scope thereof; temperatures are given in degrees Celsius; all percentages mentioned are weight percentages (w/w):

Example: 40 g of an aqueous gel containing 35 % magnesium acetate and 11 % polyvinyl alcohol (MOWIOL 4-88, Hoechst) is added with stirring (5000 rpm), to an organic solution of 10 mg zinc phthalocyanine and 1.0 g polylactic acid (MEDISORB 100 DL) in N-methyl-2-pyrrolidone (NMP) and acetone (1:9), resulting in the formation of an oil-in-water emulsion. To this emulsion pure water (40 g) is added to allow the diffusion of the organic solvents into the aqueous phase resulting in the formation of mono-dispersed polymeric nano-particles.

The nanoparticulate dispersion is then purified by cross-flow filtration using a SARTOCON Mini Device (Sartorius, Göttingen, Germany) mounted with a polyolefin cartridge filter having a 100 nm pore size. The filtration procedure is stopped after collecting 10 l of filtrate. The aqueous dispersion is finally frozen for 10 minutes at -55° and freeze-dried for 24 h at 0.05 mbar.

The lyophilisate is reconstituted in water with gentle agitation. The average particle size measured with a COULTER NANO-SIZER before purification with cross-flow filtration is 264 nm (polydispersity index: 2) and after reconstitution of the lyophilisate is 268 nm (polydispersity index: 3). The freeze-dried nanoparticles contain 0,98 % of the active agent.

What is claimed is:

1. A pharmaceutical composition suitable for the solubilization of zinc phthalocyanine characterized by the following components:
   a) the zinc phthalocyanine complex;
   b) a pharmaceutically acceptable polymer which is suitable for the formation of nanoparticles and, optionally;
   c) further pharmaceutically acceptable additives which are suitable for incorporation in a dosage form for the intended mode of administration.

2. A pharmaceutical composition according to claim 1, wherein the polymer suitable for formation of nanoparticles is a pharmaceutically acceptable homopolymer or copolymer from monomers selected from the group consisting of L-lactide N or S, D-lactide S, D,L-lactide S; or glycolide S.
3. A pharmaceutical composition according to claim 1, wherein the polymer suitable for the formation of nanoparticles is a pharmaceutically acceptable copolymer formed from monomers selected from the group consisting of methacrylic acid, methacrylic acid esters, acrylic acid and acrylic acid esters.
4. A pharmaceutical composition according to claim 1, wherein the polymer suitable for the formation of nanoparticles is a pharmaceutically acceptable cellulose derivative selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate (HPMCAS), hydroxypropyl methyl cellulose phthalate (HPMCP), cellulose acetate phthalate (CAP) and cellulose acetate trimellitate (CAT).
5. A pharmaceutical composition according to claim 3, wherein the copolymer is a 1:1- to 1:2-copolymer formed from monomers selected from the group consisting of methacrylic acid and methacrylic acid lower alkyl esters.
6. A pharmaceutical composition according to claim 5, wherein the copolymer is a 1:1- to 1:2-copolymer of methacrylic acid and methacrylic acid methyl ester.
7. A pharmaceutical composition according to claim 5, wherein the copolymer is a 1:1-copolymer of methacrylic acid and acrylic acid ethyl ester.
8. A pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable polymer b) is suitable for the formation of nanospheres.
9. A pharmaceutical composition according to claim 1, wherein the additives c) are suitable for a dosage form intended for parenteral administration.

10. A pharmaceutical composition according to claim 1, wherein the additives c) are suitable for a dosage form intended for topical administration.

11. A pharmaceutical composition for intravenous administration according to claim 1, containing

a) the zinc phthalocyanine complex;

b) a pharmaceutically acceptable homopolymer or copolymer from monomers selected from the group consisting of L-lactide N or S, D-lactide S, D,L-lactide S, or glycolide S;

c) pharmaceutically acceptable additives which are suitable for incorporation into a dosage form for intravenous administration.

12. A process for the preparation of the pharmaceutical composition according to claim 1, characterized in that an aqueous dispersion of nanoparticles is formed containing

a) the zinc phthalocyanine complex;

b) a pharmaceutically acceptable polymer which is suitable for the formation of nanoparticles;

and the dispersion is processed further with the optional addition of pharmaceutically acceptable additives c), which are suitable for incorporation into a dosage form for the intended mode of administration.

13. A process according to claim 12, characterized in that the aqueous dispersion is processed further to a lyophilisate.

14. Use of the zinc phthalocyanine complex for the preparation of a pharmaceutical dosage form containing an aqueous dispersion of nanospheres.

15. A pharmaceutical composition according to claim 1 for use in a method for treating the human or animal body by photodynamic therapy.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/51 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 633 024 (CIBA-GEIGY AG) 11 January 1995 see the whole document ---	1-15
A	EP,A,0 451 103 (CIBA-GEIGY AG) 9 October 1991 cited in the application see the whole document --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 96/03956

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 123, no. 26, 25 December 1995 Columbus, Ohio, US; abstract no. 350005, XP002020895 see abstract & EUR. J. PHARM. BIOPHARM. , vol. 41, no. 1, 1995, pages 38-43, V.LENAERTS ET AL.: "NANOCAPSULES WITH A REDUCED LIVER UPTAKE.TARGETING OF PHTHALOCYANINES TO EMT-6 MOUSE MAMMARY TUMOR IN VIVO." ---	1-15
A	CHEMICAL ABSTRACTS, vol. 123, no. 8, 21 August 1995 Columbus, Ohio, US; abstract no. 93153, XP002020896 see abstract & J. PHARM. PHARMACOL., vol. 47, no. 5, 1995, pages 382-387, E. ALLEMAN ET AL.: "PEG-COATED POLY (LACTIC) ACID NANOPARTICLES FOR THE DELIVERY OF HEXADECAFLUORO ZINC PHTHALOCYANINE TO EMT-6 MOUSE MAMMARY TUMORS." -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/EP 96/03956

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-633024	11-01-95	AU-A-	6612494	19-01-95
		CA-A-	2117399	10-01-95
		JP-A-	7053381	28-02-95
		NZ-A-	260965	21-12-95
		ZA-A-	9404952	16-01-95
EP-A-451103	09-10-91	AT-T-	108328	15-07-94
		AU-B-	634644	25-02-93
		AU-A-	7404691	10-10-91
		CA-A-	2039477	04-10-91
		DE-D-	59102143	18-08-94
		ES-T-	2056617	01-10-94
		IE-B-	64990	20-09-95
		IL-A-	97681	31-01-96
		JP-A-	4221316	11-08-92
		JP-B-	8005793	24-01-96
		US-A-	5466468	14-11-95
		US-A-	5270053	14-12-93